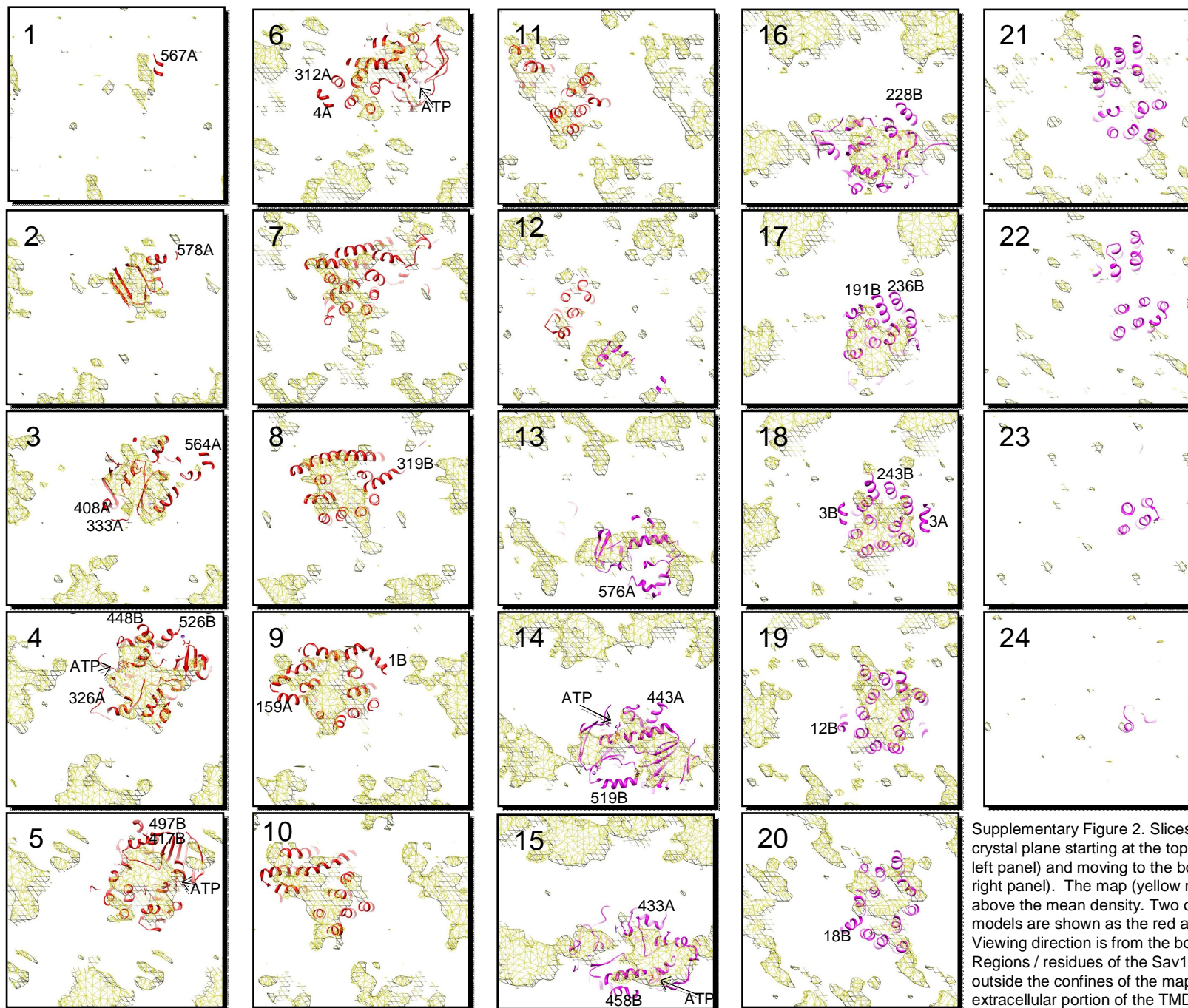


Supplementary Figure 1: Fitting of lattice lines to the experimental phase component of the crystallographic data after merging all the reflections for untilted and tilted CFTR crystals. The data for untilted crystals all lie on the $z^*=0.0$ line. Three lattice lines at increasing resolution (top to bottom) are shown. Data points are shown as 'X' or '+' with 'X' showing higher signal:noise reflections. The size of the symbol also indicates the relative amplitude. As is normal, the strength of the reflections decreases towards higher resolution. Error bars are shown for the fitting of the data. The grey boxes indicate regions of reciprocal space where data is missing or with very large errors. Structure factors obtained from such regions are weighted so that their relative contribution to the final map is minor. For the highest resolution lattice line, the extent of the resolution perpendicular to the crystal plane (i.e. along z^*) is equivalent to $1/12\text{\AA}^{-1}$.



Supplementary Figure 2. Slices, 10Å-thick, along the crystal plane starting at the top of the CFTR map (top left panel) and moving to the bottom of the map (bottom right panel). The map (yellow mesh) is displayed at 1σ above the mean density. Two of the fitted Sav1866 models are shown as the red and purple ribbon traces. Viewing direction is from the bottom of the map. Regions / residues of the Sav1866 model that lie well outside the confines of the map are as indicated. The extracellular portion of the TMD region in the lower layer of the map displays smeared weak density (sections 21-24).